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A possible role of cell cycle re-entry in epileptogenesis as observed in the abnormal plasticity of EL mice brain

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Background and Objective: We demonstrated that there was DNA fragmentation in the hippocampus of epileptic mutant EL mice, where neuronal cell loss was not found even after frequent seizures during development. The level of neurotrophic factors in hippocampus showed a significant increase in earlier developmental stage before exhibiting frequent seizures. In addition, the abundance of trophic factors could also facilitate the induction of cell division-related processes.[1-3] In the present study, we used an epileptic mutant EL mouse to examine how cyclin and corresponding cyclin dependent kinase (CDK) family are related to cell proliferation during development.

Methods: We examined the developmental changes of cyclin and corresponding CDK family, during cell cycle by Western blotting in the hippocampus in both EL mice and the control animal, DDY mice.

Results: Western blot analysis demonstrated a significant increase in levels of cyclin / CDK proteins in EL mice as compared to control DDY mice.

Discussion and Conclusion: In the present study, cell cycle regulatory proteins were investigated with respect to epileptogenesis. Passage through the four phases of the cell cycle is regulated by a family of cyclin that act as regulatory subunits of CDK. The activity of various cyclin / CDK complexes regulates the progression through G_1 / S / G_2 / M phases of the cell cycle. For cyclin / CDK expression in the hippocampus, EL mice showed an up-regulation of each cell cycle specific cyclin / CDK during early developmental stage when compared with the control DDY, suggesting that reentry of cell cycle is promoted prior to the beginning of seizures, possibly due to the abundance of neurotrophic factors, *i.e.* BDNF and NT3.[4]

Apoptotic process and cell proliferation both observed in the EL mouse brain[1-3] appear puzzling. However, in the last ten years, the concepts of neural cell loss, cell proliferation, and cell migration have dramatically changed. With respect to cell death-related proteins and neurotrophic factors in the brain, antiapoptotic Bcl-2 and proapoptotic Bax levels were increased during the periods of epileptogenesis in EL mice.[4] The neurotrohic factors NT-3 and BDNF were significant increase as Bcl-2 and Bax were increased during the epileptogenesis.[4] These lines of evidence indicate that in EL mice, the susceptibility of hippocampal neurons to "DNA fragmentation without cell loss" increases after experiencing repetitive seizures during development, probably due to a change in the balance between protective mechanism and pro-apoptotic pathway's inactivation.[4] Neurotrophic factors may play a role in epileptogenesis together with the Bcl-2 family by promoting abnormal synaptic plasticity.

In conclusion, in EL mice, during development and particularly before seizures, reentry of cell cycle is promoted possibly because of the abundance of neurotrophic factors which induce the expression of cyclin CDK. DNA fragmentation without cell loss and cell cycle reentry may work together in the process of epileptogenesis during development.

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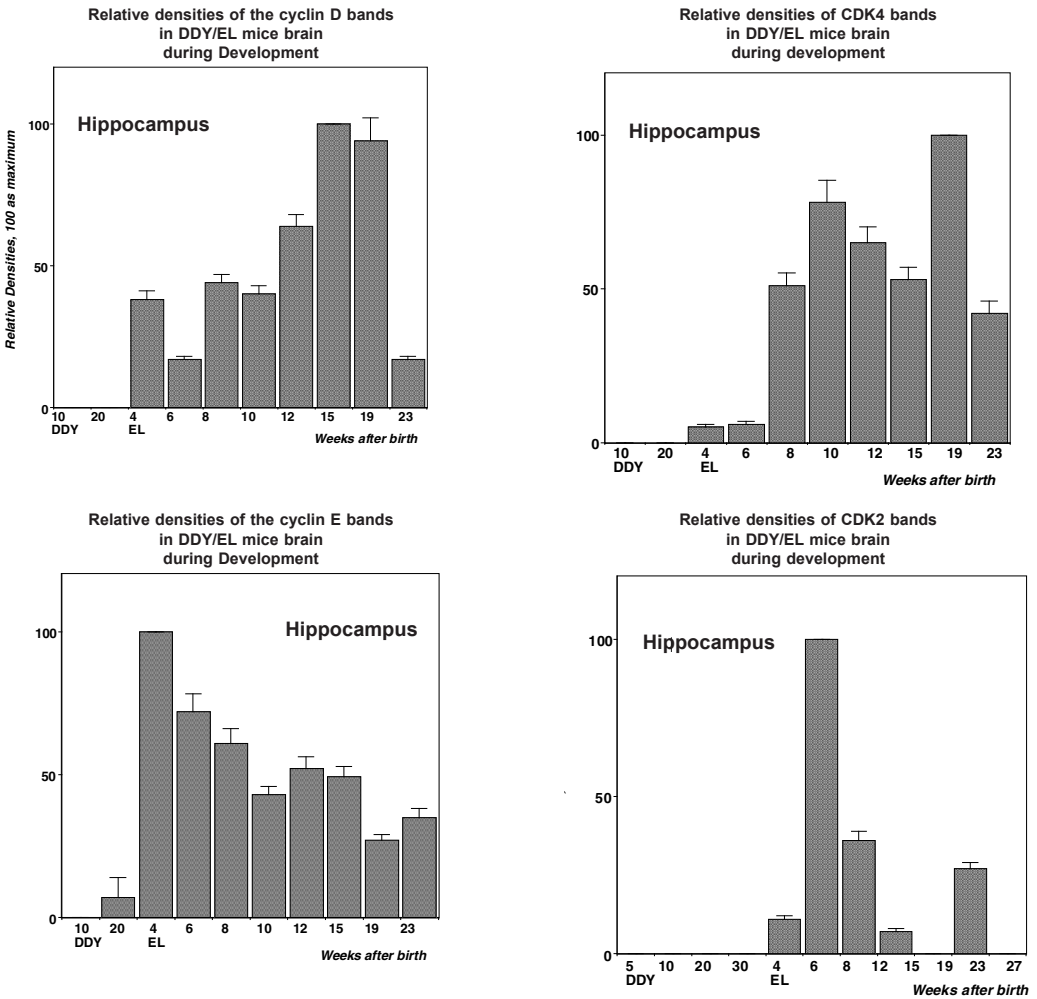

Relative expression of cyclin D,E / CDK 4,2 (G1 phase) during development in DDY /EL mice brain. Cell cycle reentry begins at G1 phase from G0 phase. Control DDY mice showed no expression at all. The expression was observed at the very early developmental stage before exhibiting seizures.